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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,088	07/18/2003	Robert P. Bennett	IVGN 332	1853

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EXAMINER	
HORNING, MICHELLE S	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,088	BENNETT ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to communication filed 1/16/2009. Any previous rejection not reiterated has been withdrawn due to claim cancellations. New claims 45-56 are under current examination.

Response to Arguments

Applicant failed to provide any arguments in response to the applied references and rejections against the claims. All claims were cancelled and Applicant provided all new claims 45-56. The Remarks provided discussions regarding safety features of the invention and the invention of the new claims.

Claim Objections-NECESSITATED BY AMENDMENTS

Claim 51 is objected to because of the following informalities: "he" of line 1 should be "The". Appropriate correction is required.

Claim Rejections - 35 USC § 112-NECESSITATED BY AMENDMENTS

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 47 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In line 1, claim 47 states "wherein the nucleic acid molecule of step (b)" of claim 45. Note that step (b) of claim 45 provides 3 separate nucleic acid molecules, including a first molecule, a second molecule and the resulting molecule following recombination. Further noted is that read in its entirety the claim does not make sense. It appears that Applicant intends to state: The method

of claim 45, wherein the first and second nucleic acids of step (b) lack sufficient homology to *prevent* homologous recombination with the three additional nucleic acid molecules and the three additional nucleic acid molecules lack sufficient homology to *prevent* homologous recombination with each other. Appropriate correction is required.

Claims 45-56 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims do not clearly set forth how the preamble of the claimed invention produces a replication-incompetent virus. How does the clamed method ultimately lead to the construction of a replication-incompetent recombinant retrovirus? The dependent claims fall therewith. Appropriate correction is required.

Claim Rejections - 35 USC § 103-NECESSITATED BY AMENDMENT

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 45-48, 50 and 52-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over von Melchner (Blut, 1988) in view of Hartley (Genome Res, 2000).

(Due to the indefinite nature of "replication incompetent" in the preamble of the claims, the claims were only examined with regard to the steps of the method.) Von Melchner describes the underlying methods of constructing a recombinant retrovirus (see whole document and p. 2-3). The retroviral DNA comprising a flanking 5' and 3' LTR integrates into the host genome to become a provirus. The 5' and 3' LTR serve as a transcriptional promoter and a regulator of polyadenylation of emerging transcripts (col. 1-2, p. 2). Von Melchner also provides that the essential viral proteins *gag*, *pol* and *env* are crucial in assembling emerging transcipts into particles and because these proteins are absent from the recombinant provirus, emerging transcripts cannot be assembled into particles (see col 2, p. 2). Thus, in order to achieve effective gene transfer via horizontal transmission requiring particle assembly, the author describes superinfecting the recombinant provirus expressing cell with wild-type retrovirus which is a psi-deleted helper proviruses encoding the essential viral proteins. The "psi" or packaging signal (see paragraph 707 of the instant specification) resides within the LTRs and its deletion leads to the failure of virus assembly of wild-type virus (col. 2, p. 2); however the psi(+) recombinant provirus is packaged (col 2, p. 2). The author describes expression of foreign genes for gene therapy, meeting the limitation of a gene

of interest and a sequence encoding a polypeptide (see col. 2, p. 3). Thus, von Melchner describes a nucleic acid molecule comprising a 5' LTR, 3' LTR and a packaging signal and separate molecules containing *gag*, *pol* and/or *env* sequences without flanking LTRs, both of which are packaged within a cell.

Von Melchner does not teach recombination sites comprising either *att*R sites or *att*L sites on two separate molecules, a lack of sufficient homology to prevent homologous recombination between the first or second nucleic acid molecule with the three additional nucleic acids, an origin of replication, a selectable marker and a restriction site between recombination sites.

Hartley describes DNA cloning using site-specific recombination between two molecules (see whole document). See Figure 1B which depicts two separate DNA molecules in which one molecule contains 2 *att*L sites and a gene of interest and the other contains 2 *att*R sites. Page 1789 provides that the molecules encode either kanamycin or ampicillin resistance genes, meeting the limitation of a selectable marker. Following recombination, an expression clone is produced and E. coli transformants with this molecule are ampicillin resistant. The legend to Figure 3 describes the unique NcoI site and the T7 promoter of the destination vector. Also, there must also inherently be an origin of replication given the DNA is copied following transformation of bacterial cells (see p. 1791, col. 2 and minipreps, p. 1795). The author describes the *in vitro* site-specific recombination method as a method allowing numerous DNA segments to be transferred in parallel into many vector backgrounds for the in-dept functional analysis of genes and rapid optimization of protein expression (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further include the method steps taught by Hartley in combination with the method steps taught by von Melchner because *in vitro* site-specific recombination allows for multiple DNA segments such as genes of interest to be transferred in the different vector backgrounds such as viral DNA or retroviruses. Also, it would have been obvious for the ordinary artisan to prevent separate DNA molecules from undesired homologous recombination for optimization of results.

Claims 45, 46 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over von Melchner in view of Hartley as applied to claims 45-48, 50 and 52-56 above, and further in view of Ping (RNA, 1997) and Hopkins (PNAS, 1993).

As set forth above, Von Melchner and Hartley teach recombinant retroviruses packaged within a cell and *in vitro* site-specific recombination.

However, the combined teachings fail to disclose a retroviral rev gene or a VSV-G gene.

Ping describes that the gene expression of HIV-1 depends on the interactions of viral regulatory proteins, Tat and Rev. Specifically, Rev acts postranscriptionally to increase the cytoplasmic accumulation of the viral gag-pol and env mRNA (see Introduction).

Hopkins discloses that retroviruses use specific cell surface proteins as receptors to get into cells and attach to the receptors via their envelope glycoproteins, which may be tissue specific. As a result, retroviruses have a limited host range. In contrast, VSV

has a notoriously broad host range and VSV G glycoprotein is responsible for the viral host range (p. 8759). Hopkins describes the Moloney/VSV-G pseudotype as having a broad host range (p. 8760).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further include a rev gene in the methods taught by von Melchner and Hartley. One would have been motivated to do so in order to increase the cytoplasmic accumulation of the viral gag-pol and env mRNA particularly for HIV-1. Further, the ordinary artisan would have used the VSV G glycoproteins in the methods taught by von Melchner and Hartley in order to increase the host range of a pseudotyped retrovirus.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/M. H./
Examiner, Art Unit 1648

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646